

09/546,857 Listing of Claims:

Claims 1-56 (canceled)

44

Claim 57 (currently amended): A variant of human VEGF comprising amino acid substitutions D63S, G65M, and L66R, wherein the variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

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Claim 58 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 57.

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Claim 59 (previously presented): A vector comprising the nucleic acid of claim 58.

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Claim 60 (currently amended): A variant of human VEGF comprising one or more non-conservative amino acid substitution(s) at residues 63 to 66 and one or more amino acid substitution(s) at residues 18, 21, 22, or 25, wherein the VEGF variant exhibits selective binding affinity for KDR receptor a higher KDR to Flt-1 binding ratio as compared with native VEGF.

18

Claim 61 (currently amended): The VEGF variant of claim 60, wherein at least one of the amino acid substitution(s) comprises D63S, G65M, or L66R.

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Claim 62 (currently amended): The VEGF variant of claim 60, wherein at least one of the amino acid substitution(s) comprises M18E, Y21L, Q22R, or Y25S.

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Claim 63 (previously presented): The VEGF variant of claim 60, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

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Claim 64 (previously presented): The VEGF variant of claim 60, wherein the amino acid substitutions comprise D63S, G65M, and L66R.

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 Claim 65 (currently amended): The VEGF variant of claim 64, wherein at least one of the amino acid substitution(s) comprise M18E, Y21L, Q22R, or Y25S.

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 Claim 66 (currently amended): The VEGF variant of claim 64, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

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 Claim 67 (currently amended): A The VEGF variant of claim 60, comprising one of the following combinations of amino acid substitutions:

- (a) M18E, D63S, G65M, and L66R;
- (b) Y21L, D63S, G65M, and L66R;
- (c) Q22R, D63S, G65M, and L66R;
- (d) Y25S, D63S, G65M, and L66R;
- (e) M18E, Y21L, D63S, G65M, and L66R;
- (f) M18E, Q22R, D63S, G65M, and L66R;
- (g) M18E, Y25S, D63S, G65M, and L66R;
- (h) Y21L, Q22R, D63S, G65M, and L66R;
- (i) Y21L, Y25S, D63S, G65M, and L66R;
- (j) Q22R, Y25S, D63S, G65M, and L66R;
- (k) M18E, Y21L, Q22R, D63S, G65M, and L66R;
- (l) M18E, Q22R, Y25S, D63S, G65M, and L66R;
- (m) Y21L, Q22R, Y25S, D63S, G65M, and L66R;
- (n) M18E, Y21L, Q22R, Y25S, and D63S;
- (o) M18E, Y21L, Q22R, Y25S, and G65M;
- (p) M18E, Y21L, Q22R, Y25S, and L66R;
- (q) M18E, Y21L, Q22R, Y25S, D63S, and G65M;
- (r) M18E, Y21L, Q22R, Y25S, D63S, and L66R;
- (s) M18E, Y21L, Q22R, Y25S, G65M, and L66R; or
- (t) M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.

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 Claim 68 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 60.

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Claim 69 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 3.

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Claim 70 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 28.

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Claim 71 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 29.

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Claim 72 (previously presented): A vector comprising the nucleic acid of claim 6.

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Claim 73 (previously presented): A host cell comprising the vector of claim 72.

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Claim 74 (previously presented): A composition comprising the VEGF variant of claim 68 and a carrier.

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Claim 75 (previously presented): The composition of claim 74, wherein the carrier is a pharmaceutically acceptable carrier.

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Claim 76 (previously presented): An assay for detecting KDR receptor, comprising contacting an isolated cell or tissue with a VEGF variant of claim 60 and assaying for binding of the VEGF variant to the cell or tissue.

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Claim 77 (previously presented): A method for stimulating phosphorylation of a KDR receptor, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of the KDR receptor.

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Claim 78 (previously presented): A method for stimulating MAP kinase activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of MAP kinase.

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Claim 79 (previously presented): A method for stimulating PLC-gamma activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of PLC-gamma.

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Claim 80 (previously presented) A method for stimulating PI 3'-kinase activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of PI 3'-kinase.

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Claim 81 (previously presented): A method for stimulating vasculogenesis or angiogenesis, comprising contacting endothelial cells expressing KDR receptor with an effective amount of a VEGF variant of claim 60.

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Claim 82 (previously presented): A method for promoting the migration of endothelial cells, comprising contacting endothelial cells expressing KDR receptor with an effective amount of a VEGF variant of claim 60.

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Claim 83 (currently amended): A variant of human VEGF comprising two or more amino acid substitutions at residues 17 to 25, wherein the VEGF variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

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Claim 84 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise two or more amino acid substitutions at residues 18, 21, 22, or 25.

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Claim 85 (currently amended): The VEGF variant of claim 83, wherein at least one of the amino acid substitution(s) comprise M18E, Y21L, Q22R, or Y25S.

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Claim 86 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

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Claim *81* (previously presented): The VEGF variant of claim *83*, wherein the amino acid substitutions comprise F17I, M18E, Y21F, Q22K, and Y25S.

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Claim *88* (previously presented): The VEGF variant of claim *83*, wherein the amino acid substitutions comprise F17I, M18E, Y21F, Q22E, and Y25I.

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Claim *89* (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim *83*.

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Claim *90* (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim *83*.

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Claim *91* (previously presented): The VEGF variant of claim *60*, wherein the amino acid substitutions further comprise a substitution at residue *17*.

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Claim *92* (currently amended): A variant of human VEGF, comprising:
(a) one or more amino acid substitution(s) at residues 17-25, and
(b) one or more amino acid substitution(s) at residues 63-66;

wherein amino acid residue 60 is cysteine, and the variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

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Claim *93* (new): The VEGF variant of claim *63*, comprising amino acid substitutions Y21L, D63S, G65M, and L66R.

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Claim *94* (new): The VEGF variant of claim *63*, comprising amino acid substitutions Q22R, D63S, G65M, and L66R.

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Claim *95* (new): The VEGF variant of claim *63*, comprising amino acid substitutions Y25S, D63S, G65M, and L66R.

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Claim *96* (new): The VEGF variant of claim *63*, comprising amino acid substitutions M18E, Y21L, D63S, G65M, and L66R.

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Claim *97* (new): The VEGF variant of claim *65*, comprising amino acid substitutions M18E, Q22R, D63S, G65M, and L66R.

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Claim *98* (new): The VEGF variant of claim *65*, comprising amino acid substitutions M18E, Y25S, D63S, G65M, and L66R.

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Claim *99* (new): The VEGF variant of claim *65*, comprising amino acid substitutions Y21L, Q22R, D63S, G65M, and L66R.

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Claim *100* (new): The VEGF variant of claim *65*, comprising amino acid substitutions Y21L, Y25S, D63S, G65M, and L66R.

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Claim *101* (new): The VEGF variant of claim *65*, comprising amino acid substitutions Q22R, Y25S, D63S, G65M, and L66R.

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Claim *102* (new): The VEGF variant of claim *65*, comprising amino acid substitutions M18E, Y21L, Q22R, D63S, G65M, and L66R.

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Claim *103* (new): The VEGF variant of claim *65*, comprising amino acid substitutions M18E, Q22R, Y25S, D63S, G65M, and L66R.

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Claim *104* (new): The VEGF variant of claim *65*, comprising amino acid substitutions Y21L, Q22R, Y25S, D63S, G65M, and L66R.

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Claim *105* (new): The VEGF variant of claim *66*, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and D63S.

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Claim *106* (new): The VEGF variant of claim *66*, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and G65M.

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Claim *107* (new): The VEGF variant of claim *66*, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and L66R.

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Claim *108* (new): The VEGF variant of claim *66*, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, D63S, and G65M.

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Claims 1-56 (canceled)

Claim 57 (currently amended): A variant of human VEGF comprising amino acid substitutions D63S, G65M, and L66R, wherein the variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

Claim 58 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 57.

Claim 59 (previously presented): A vector comprising the nucleic acid of claim 58.

Claim 60 (currently amended): A variant of human VEGF comprising one or more non-conservative amino acid substitution(s) at residues 63 to 66 and one or more amino acid substitution(s) at residues 18, 21, 22, or 25, wherein the VEGF variant exhibits selective binding affinity for KDR receptor a higher KDR to Flt-1 binding ratio as compared with native VEGF.

Claim 61 (currently amended): The VEGF variant of claim 60, wherein at least one of the amino acid substitution(s) comprises D63S, G65M, or L66R.

Claim 62 (currently amended): The VEGF variant of claim 60, wherein at least one of the amino acid substitution(s) comprises M18E, Y21L, Q22R, or Y25S.

Claim 63 (previously presented): The VEGF variant of claim 60, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

Claim 64 (previously presented): The VEGF variant of claim 60 wherein the amino acid substitutions comprise D63S, G65M, and L66R.

Claim 65 (currently amended): The VEGF variant of claim 64, wherein at least one of the amino acid substitution(s) comprise M18E, Y21L, Q22R, or Y25S.

Claim 66 (currently amended): The VEGF variant of claim 64, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

Claim 67 (currently amended): AThe VEGF variant of claim 60, comprising one of the following combinations of amino acid substitutions:

- ____ (a) M18E, D63S, G65M, and L66R;
- ____ (b) Y21L, D63S, G65M, and L66R;
- ____ (c) Q22R, D63S, G65M, and L66R;
- ____ (d) Y25S, D63S, G65M, and L66R;
- ____ (e) M18E, Y21L, D63S, G65M, and L66R;
- ____ (f) M18E, Q22R, D63S, G65M, and L66R;
- ____ (g) M18E, Y25S, D63S, G65M, and L66R;
- ____ (h) Y21L, Q22R, D63S, G65M, and L66R;
- ____ (i) Y21L, Y25S, D63S, G65M, and L66R;
- ____ (j) Q22R, Y25S, D63S, G65M, and L66R;
- ____ (k) M18E, Y21L, Q22R, D63S, G65M, and L66R;
- ____ (l) M18E, Q22R, Y25S, D63S, G65M, and L66R;
- ____ (m) Y21L, Q22R, Y25S, D63S, G65M, and L66R;
- ____ (n) M18E, Y21L, Q22R, Y25S, and D63S;
- ____ (o) M18E, Y21L, Q22R, Y25S, and G65M;
- ____ (p) M18E, Y21L, Q22R, Y25S, and L66R;
- ____ (q) M18E, Y21L, Q22R, Y25S, D63S, and G65M;
- ____ (r) M18E, Y21L, Q22R, Y25S, D63S, and L66R;
- ____ (s) M18E, Y21L, Q22R, Y25S, G65M, and L66R; or
- ____ (t) M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.

Claim 68 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 60.

Claim 69 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 63.

Claim 70 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 65.

Claim 71 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 67.

Claim 72 (previously presented): A vector comprising the nucleic acid of claim 68.

Claim 73 (previously presented): A host cell comprising the vector of claim 72.

Claim 74 (previously presented): A composition comprising the VEGF variant of claim 60 and a carrier.

Claim 75 (previously presented): The composition of claim 74, wherein the carrier is a pharmaceutically acceptable carrier.

Claim 76 (previously presented): An assay for detecting KDR receptor, comprising contacting an isolated cell or tissue with a VEGF variant of claim 60 and assaying for binding of the VEGF variant to the cell or tissue.

Claim 77 (previously presented): A method for stimulating phosphorylation of a KDR receptor, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of the KDR receptor.

Claim 78 (previously presented): A method for stimulating MAP kinase activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of MAP kinase.

Claim 79 (previously presented): A method for stimulating PLC-gamma activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of PLC-gamma.

Claim 80 (previously presented) A method for stimulating PI 3'-kinase activation, comprising contacting a cell with a VEGF variant of claim 60 in amount effective to stimulate phosphorylation of PI 3'-kinase.

Claim 81 (previously presented): A method for stimulating vasculogenesis or angiogenesis, comprising contacting endothelial cells expressing KDR receptor with an effective amount of a VEGF variant of claim 60.

Claim 82 (previously presented): A method for promoting the migration of endothelial cells, comprising contacting endothelial cells expressing KDR receptor with an effective amount of a VEGF variant of claim 60.

Claim 83 (currently amended): A variant of human VEGF comprising two or more amino acid substitutions at residues 17 to 25, wherein the VEGF variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

Claim 84 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise two or more amino acid substitutions at residues 18, 21, 22, or 25.

Claim 85 (currently amended): The VEGF variant of claim 83, wherein at least one of the amino acid substitution(s) comprise M18E, Y21L, Q22R, or Y25S.

Claim 86 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise M18E, Y21L, Q22R, and Y25S.

Claim 87 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise F17I, M18E, Y21F, Q22K, and Y25S.

Claim 88 (previously presented): The VEGF variant of claim 83, wherein the amino acid substitutions comprise F17I, M18E, Y21F, Q22E, and Y25I.

Claim 89 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 83.

Claim 90 (previously presented): An isolated nucleic acid sequence encoding the VEGF variant of claim 86.

Claim 91 (previously presented): The VEGF variant of claim 60, wherein the amino acid substitutions further comprise a substitution at residue 17.

Claim 92 (currently amended): A variant of human VEGF, comprising:

- (a) one or more amino acid substitution(s) at residues 17-25, and
- (b) one or more amino acid substitution(s) at residues 63-66;

wherein amino acid residue 60 is cysteine, and the variant exhibits a higher KDR to Flt-1 binding ratio as compared with native VEGF.

Claim 93 (new): The VEGF variant of claim 65, comprising amino acid substitutions Y21L, D63S, G65M, and L66R.

Claim 94 (new): The VEGF variant of claim 65, comprising amino acid substitutions Q22R, D63S, G65M, and L66R.

Claim 95 (new): The VEGF variant of claim 65, comprising amino acid substitutions Y25S, D63S, G65M, and L66R.

Claim 96 (new): The VEGF variant of claim 65, comprising amino acid substitutions M18E, Y21L, D63S, G65M, and L66R.

Claim 97 (new): The VEGF variant of claim 65, comprising amino acid substitutions M18E, Q22R, D63S, G65M, and L66R.

Claim 98 (new): The VEGF variant of claim 65, comprising amino acid substitutions M18E, Y25S, D63S, G65M, and L66R.

Claim 99 (new): The VEGF variant of claim 65, comprising amino acid substitutions Y21L, Q22R, D63S, G65M, and L66R.

Claim 100 (new): The VEGF variant of claim 65, comprising amino acid substitutions Y21L, Y25S, D63S, G65M, and L66R.

Claim 101 (new): The VEGF variant of claim 65, comprising amino acid substitutions Q22R, Y25S, D63S, G65M, and L66R.

Claim 102 (new): The VEGF variant of claim 65, comprising amino acid substitutions M18E, Y21L, Q22R, D63S, G65M, and L66R.

Claim 103 (new): The VEGF variant of claim 65, comprising amino acid substitutions M18E, Q22R, Y25S, D63S, G65M, and L66R.

Claim 104 (new): The VEGF variant of claim 65, comprising amino acid substitutions Y21L, Q22R, Y25S, D63S, G65M, and L66R.

Claim 105 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and D63S.

Claim 106 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and G65M.

Claim 107 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, and L66R.

Claim 108 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, D63S, and G65M.

Claim 109 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, D63S, and L66R.

Claim 110 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, G65M, and L66R.

Claim 111 (new): The VEGF variant of claim 66, comprising amino acid substitutions M18E, Y21L, Q22R, Y25S, D63S, G65M, and L66R.

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